Medical and Pediatric Oncology 28:348–354 (1997)

Survival and Late Effects in Medulloblastoma Patients Treated With Craniospinal Irradiation Under Three Years Old

A.E. Kiltie, MA, MRCP(UK), FRCR, **L.S. Lashford,** MRCP, PhD, **and H.R. Gattamaneni,** MD, FRCR*

Conventional treatment of medulloblastoma has involved surgery to the primary tumour and radiotherapy to the primary site and craniospinal axis. However CNS irradiation in a young child may result in significant side effects. Thus new treatment strategies have emerged which include chemotherapy, given in order to delay radiotherapy, to enable radiation dose reduction to the primary site and craniospinal axis, or even to eliminate radiotherapy completely. Such treatments have not yet been adequately evaluated in terms of survival and late effects. We report a retrospective study of 37 patients under the age of 36 months treated with postoperative craniospinal irradiation, in which the radiation dose to the neuroaxis was below conventional dosage. The overall actuarial 10-year survival rate was 44% and the actuarial 10-year relapse free survival rate was 54%. Both radiotherapy and chemotherapy contributed to morbidity and mortality. Four of 16 patients who survived longer than 10 years had no hard neurological signs; all but one patient have required extra support at school. Of nine patients available for work, two have obtained employment but only one has maintained this. No young adults have married. Despite lower doses of radiation, all but 1 survivor has significant spine shortening, and all who reached final height were short. Further work is needed to complete the profile of late effects in this group, which should include the survivors own perceptions of quality of life. It is hoped that multimodality treatment and supportive care can sustain acceptable survival rates but reduce the burden of late effects. Med. Pediatr. Oncol. 28:348–354, 1997.

Key words: brain tumours; chemotherapy; children; medulloblastoma; radiotherapy

INTRODUCTION

Medulloblastoma accounts for 20–25% of all childhood intracranial malignancy [1]. With primary surgery and adjuvant radiotherapy most pediatric studies achieve a 5-year survival rate of approximately 50% [2]. Unfortunately, curative radiotherapy is often associated with significant late effects. These include endocrine abnormalities, impaired spinal growth, and neuropsychological dysfunction. Numerous studies have shown that the severity of the late effects are inversely related to the age at which radiation is undertaken. Very young children (under the age of three years) are felt to be particularly vulnerable to radiation damage [3] and a number of international and national treatment regimens are assessing adjuvant chemotherapy in an attempt to delay or avoid radiotherapy [4].

A number of competing issues need to be taken into account when evaluating the use of chemotherapy. These include the fact that medulloblastoma presenting in children under the age of three can be cured with surgery and standard radiotherapy [2]. Whilst young children may have lower 5-year survival rates when compared to older children, survival at 10 years is similar. Secondly, chemotherapy without radiotherapy may not be adequate treatment for medulloblastoma and radiotherapy given in combination with chemotherapy may be more toxic than radiotherapy alone. Many of these issues will become clearer as the children treated on the newer treatment protocols survive to reveal late complications of treatment. These will need to be carefully compared with the health status of survivors treated with the ''gold standard'' of surgery and radiotherapy.

The purpose of this study is to report on the survival and late effects of reduced craniospinal irradiation with or without chemotherapy in children under the age of 36 months with medulloblastoma, at the Christie Hospital from 1956–1988.

STUDY POPULATION

The case notes of all children less than 36-months-old at the commencement of radiotherapy who presented to the Christie Hospital with medulloblastoma from 1956–1988 were reviewed. During the study period 40 patients were referred, and 37 of these patients received craniospinal irradiation. Of those who did not, one had local

Christie Hospital NHS Trust, Manchester, United Kingdom.

*Correspondence to: Dr. H.R. Gattamaneni, Christie Hospital NHS Trust, Wilmslow Road, Manchester M20 9BX.

Received 5 May 1995; Accepted 14 August 1996

TABLE I. Radiotherapy Techniques and Dosages

Years	Energy	Number	Dose to CSA	Days	Dose to PF	Days
1956–60	kV	4	27–30Gy in 17#	22–24 days	5–10Gy	Concurrent with CSI
pre-1972	kV + MV	13	27Gy in 17#	22–27 days	8–11Gy	Concurrent with CSI
		+2	interrupted due to infection			
1972–83	MV	8	20–35Gy in 20#	28 days	15Gy in 10#	13–14 days
		+3	interrupted due to infection (mean 28Gy; med 30Gy)			
1984–88	MV	7	20–30Gy in 20# (mean 25Gy; med 25Gy)	25–29 days	20Gy in 10#	13–14 days

CSA = craniospinal axis; CSI = craniospinal irradiation; PF = posterior fossa.

irradiation alone and two died in the postoperative period, either before or at the start of radiotherapy. These 3 patients were not included in the subsequent analysis.

Of the remaining 37 patients, 24 patients were male; 13 were female. The median age at which radiotherapy was started was 24 months (range 5–35). All patients had histological confirmation of the diagnosis, either at presentation or at postmortem. Patients did not have routine assessment for craniospinal disease. Sixteen patients underwent CT scanning of the brain, 5 had myelograms all of which were normal and 6 had their CSF examined histologically. Two patients had abnormal CSF cytology and one other patient was noted to have nodules on the cerebellum at operation. Otherwise no patient was known to have metastases at presentation.

Surgery

Four patients were assessed by the surgeon as having a complete resection, 22 patients underwent subtotal resection (definition as per the SIOP I study) [5], four had partial excisions, two underwent biopsy only, and four had decompressions (three with biopsy). One patient had no operation other than a shunt insertion. There were six postoperative CSF infections and one wound infection. Ten patients required an intracranial shunt. The median time from surgery to radiotherapy was 15.5 days (range 2–70).

Radiotherapy

The radiotherapy technique changed over the study period [6,7]. Four cases from 1956–1960 were treated with a single posterior kilovoltage field and anterior or lateral kilovoltage fields to supplement the head dose (see Table I). In the 15 remaining pre-1972 cases the anterior head build up was achieved by anterior oblique wedged megavoltage fields (old technique). From 1972 onwards patients received 4 weeks' treatment to the cranium and cervical cord using a lateral parallel opposed pair, with the rest of the spine being treated with angled wedged fields, and a two week boost being delivered to the posterior fossa. Until 1983 the posterior fossa boost dose was 15Gy, but this was subsequently increased to 20Gy.

Chemotherapy

From 1970–1986, all 15 patients received adjuvant chemotherapy (see Table II).

Actuarial survival rates were calculated using the Kaplan-Meier method, with the Log-Rank test used for comparisons. Patients were followed up after treatment in outpatient clinics initially at 3 monthly intervals, and then with decreasing frequency annually after 5 years. At each visit, patients were questioned and examined for evidence of recurrence of their medulloblastoma and for late effects of the treatment, and such findings were documented in the case notes. The majority of survivors underwent formal endocrine assessment. The majority of patients are still on regular follow-ups at the hospital, but three long-term survivors have moved out of the area and are kept on long-term follow-up by correspondence.

RESULTS

Survival

An univariate analysis of treatment factors and survival was performed. The overall 5-year actuarial survival rate was 44.5% with approximately 95% CI (28.1%,59.7%) using Greenwood's formula (figure 1). There were no deaths between 5 and 10 years, hence 10-year survival rates were the same. Neither sex nor age at the time of treatment (above or below 2 years) appeared to have a substantial impact on survival. [Overall actuarial survival for males at 5 years 48%, females 38%; under 2 years 47%, over 2 years 40%]. A number of treatment factors were examined for their impact on 5-year survival. These included completeness of resection (patients with sub-total resection or better, 52% vs. lesser surgery, 27%), radiotherapy technique (old technique, 42% vs. megavoltage technique, 47%), and administration of adjuvant vincristine (receiving vincris-

TABLE II. Chemotherapy Administered

Number of patients	Drugs	Dose	Schedule
15	Vincristine with XRT	1.5–2mg/m^2	weekly × 3
3	Vincristine post-XRT	1.5mg/m^2	× 4–8
4	BCNU (+/− VCR)	BCNU 100mg/m^2 VCR 2mg/m^2	6 weekly for 1–2 years
1	MTX, VM26, Procarbazine	pre-XRT	pre-XRT
1	SIOP sandwich (low risk)	see [14]	
1	VCR, CCNU	CCNU 40mg/m^2 VCR 1.5mg/m^2 Day 1, 8, 15	6 weekly × 8
1	CCNU, procarbazine (at relapse)		×1

VCR = vincristine; MTX = methotrexate; XRT = radiotherapy.

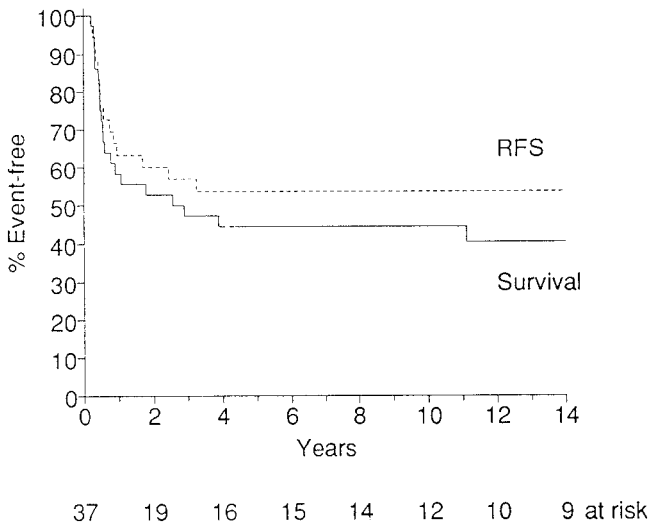

Fig. 1. Survival and relapse-free survival in patients treated with craniospinal irradiation.

tine, 46.7% vs. no vincristine, 45.1%). None of the above comparisons were significant in a two-tailed log rank test. However, given the small size of the series, any differences would have to be very large (of the order 30–40% in 5-year survival) to have a reasonable chance of detection.

Of 4 patients receiving 20Gy to the CSA, 3 are still alive (1 tumour death), of 4 given 25Gy, 3 are alive (1 chemotherapy related death), of 9 patients given 30Gy, 8 are dead (5 from tumour related deaths), and one patient given 35Gy died from BCNU-related pulmonary fibrosis. All patients who experienced delays in the administration of radiotherapy died, 5 due to tumour relapse, (median delay 6.5 days, range 1–44 days, n = 6).

Relapses

All patients who relapsed died of disease. The overall actuarial relapse-free survival rate at 5 years was 54% (figure 1). Proportionally more patients relapsed treated with the old radiotherapy technique (50%) compared with megavoltage radiation (31%). Moreover, systemic metastases were only seen in patients treated with the old technique (in three patients who incidentally did not have shunts in situ). In patients treated with megavoltage radiotherapy, the median total posterior fossa dose was 45Gy in both those patients who had posterior fossa relapse and those who achieved local control, but there were fewer relapses in patients given a 20Gy boost to the posterior fossa than those given 15Gy (table III). Unfortunately the earlier patients did not undergo CT scanning at relapse and none had MRI scans performed, hence site of relapse was recorded from clinical and/or postmortem findings only.

Non-tumour deaths

There were 7 non-tumour deaths, 6 of which were related to acute or chronic lung toxicity. In the immediate posttreatment period there were 2 deaths from pneumonitis and a third from acute pulmonary oedema during severe neutropenia. Three of 4 patients who received BCNU as part of their adjuvant chemotherapy died of delayed lung fibrosis 2, 11, and 20 years from therapy. Pulmonary function tests showed a restrictive spirometric pattern in these patients [8]. The seventh patient died with meningitis, complicating a shunt infection and there was an eighth late death in a male patient with Gorlin's syndrome. This patient died with multiple basal cell and squamous cell carcinomas 30 years after treatment.

Neurological late effects

These were documented for the 13 patients who are still alive and for 3 patients who died but were followed up for more than 10 years. Four had no residual deficit. As might be expected the major problem was residual ataxia (10 patients). All could walk and feed themselves. Three had residual epilepsy, 2 cranial nerve signs, 1 optic atrophy, 1 was blind in his left eye, 1 had long tract signs, and 1 had persistent involuntary movements. One patient

TABLE III. Site of First Recurrence vs. Technique

	Megavoltage			
	kV/kV+MV	1500cGy	2000cGy	total
Posterior fossa alone	5	2	0	7
Posterior fossa and supratentorial	0	0	1	1
Posterior fossa and spinal canal	1	1	0	2
Spinal canal alone	0	1	0	1
CNS unspecified	1	1	0	2
ExtraCNS	1	0	0	1
CNS + extraCNS	1	0	0	1
	9	5	1	15

had bladder paralysis requiring urinary diversion which was not thought to be due to the diagnosis or treatment of the medulloblastoma.

Growth

All five patients followed up to final height are short (mean SD score −4.2, range −3.9 to −4.7) and all had spine shortening (mean SD difference of subischial leg length less sitting height +4.5, range +3.4 to +5.1) (See Table IV). The remaining seven patients followed up for over 5 years also tended to be short (mean SD score −1.3, range −6.2 to +0.6) and to have spine shortening (mean SD difference +2.9, range +1.5 to +5.2). Provocative growth hormone testing using the insulin tolerance test was performed in 11 of those patients followed up for more than 5 years. Eight patients required growth hormone, and two other patients were documented as having partial growth hormone deficiency (defined as a response of 7–15 mU/l peak growth hormone response to insulin). One patient did not have growth hormone deficiency (prepubertal male) and five did not have growth hormone status documented.

Endocrine

Of the ten patients where the onset of puberty was documented, 4 have had early onset (3 male and 1 female) at ages 8.6, 8.7, 9.6, and 8.5 respectively. Two male patients have received the GnRH analogue, goserelin in an attempt to increase final height. Additionally two patients have developed multinodular goitre and have required thyroidectomy, a third developed biochemical hypothyroidism (all three treated with kilovoltage radiotherapy) and a fourth, now dead, (treated with megavoltage radiotherapy) had clinical hypothyroidism.

Second tumours

One patient had a thyroid adenoma, and 3 had Gorlin's syndrome with multiple basal cell carcinomas (and squamous cell carcinomas in one patient). No other second tumours were recorded.

Social attainments

Of the 13 patients who are still alive and a further 3 who survived 10 years after treatment, 10 are known to have attended a normal school albeit with learning difficulties. Six patients have required placement in educational establishments that cater for special learning or physical needs. Nine have reached an age at which they are available for work; 2 have obtained employment and one of these has held down a job. None of these young adults has married. Full scale intelligence quotient was not routinely tested formally in these patients. (See Table V.)

Miscellaneous

One female patient required a brace for kyphosis, two were noted to have possible radiotherapy-related dental caries, and one had cataracts. All were treated with kilovoltage radiotherapy. One Gorlin's patient treated with megavoltage radiotherapy had osteopenia with limb fractures.

DISCUSSION

The management of very young children with medulloblastoma remains a contentious issue. Standard treatment with surgery and irradiation undoubtedly carries a significant burden of late effects. The range and severity of these late effects have influenced decisions regarding treatment with radiotherapy and drives the current search for chemotherapy-based treatment strategies. These concerns are seen right across the spectrum of CNS tumours but are most sharply focussed in infants with medulloblastoma where full neuraxis irradiation is required for long-term survival. Survival of young patients with medulloblastoma has always been poor [1,9,10,11,12]. The 5-year actuarial survival of British children aged 0–2 years diagnosed with medulloblastoma during the years 1971–1985 was 13%. One important factor influencing the poor survival would appear to be decisions about treatment, as 31% of all children with CNS tumours under the age of two years died either untreated or with surgery alone. Similar results have been reported from population based studies in the United States of America.

The cohort of patients reported in this study represents 73% of children diagnosed with medulloblastoma in the North West Region during the years 1956–1988 (NW Children's Cancer Registry). The remaining children either died at the time of initial presentation or within the immediate postoperative period. The results provide information on two recurring themes in the management of infant medulloblastoma, long-term survival when treated with curative intent and the severity of the late effects of a treatment strategy containing postoperative cranisopinal irradiation. Of course the study

TABLE IV. Endocrine Effects and Quality of Life

Patient	Year	Sex	Age at XRT in months	CSI dose	Age at puberty (years)	GH (at age)	Short stature SDS	Spine shortening SD diff	Leg length SD	At age (years)
1	1957	m	29	2700	?					
2	1958	m	33	2700	?					
3	1963	m	34	2700	?					
4	1965	m	25	2700	12.6	yes (12.9)	−4.0	+5.1	−1.0	28.0
5	1968	f	15	2700	?	no (partial deficiency)	−3.9	+4.3	−1.2	22.6
6	1968	m	33	2700	?	?	+0.2	−1.3	−0.4	7.6
7	1968	f	15	2700	8.5[a]	yes (8.7)	−4.4	+5.1	−1.3	23.8
8	1970	f	17	2700[b]	9.3	no (partial deficiency)	−4.7	+3.5	−2.2	24.4
9	1972	m	21	3000[c]	9.6[a]	yes (9.9)	−4.0	+4.5	−1.3	17.9
10	1975	f	29	3000[c]	10.1	yes (7.4)	−6.2	+2.4	−3.6	13.3
11	1982	m	18	2500[c]	?	no	−1.0	+4.5	+1.1	13.6
12	1983	m	17	2000[b]	10.5 (G)	yes (7.4)	−0.1	+2.6	+1.1	11.5
13	1984	m	24	2500[b]	8.7 (G)[a]	yes (4.5)	+0.6	+5.2	+2.9	11.8
14	1985	m	6	2000[c]	8.6[a]	yes (2.9)	−0.5	+2.2	+0.4	9.2
15	1986	m	14	2000	not yet	no	−1.9	+1.5	−1.0	8.9
16	1988	f	20	2500	not yet	yes (3.7)	−0.3	+2.1	+0.6	7.3

[a] = early onset of puberty.
[b] = vincristine.
[c] = vincristine + other chemotherapy.
G = GNRH analogue.

TABLE V. Social Attainments

Patient	Sex	Age at treatment (months)	Age at followup (years)	Schooling	Work	Married	Notes
1	M	29	32 (dead)	For physically handicapped	?	no	Gorlin's
2	M	33	36	Special classes, normal school	Unemployed	no	
3	M	34	32	Special school	Unemployed	no	
4	M	25	30	Normal school, remedial lessons	Lost job due to poor performance	no	
5	F	15	27	Special school (IQ 50)	Unemployed	no	Gorlin's
6	M	33	24	Normal school, poor performance	?	no	On written followup
7	F	15	26	Special school	Unemployed	no	Troublesome fits
8	F	17	25	Special school, college-can type	Unemployed living independently	no	
9	M	21	22 (dead)	No learning difficulties	Glass polisher	no	BCNU fibrosis
10	F	29	13 (dead)	Normal school, remedial lessons	NA	NA	BCNU fibrosis
11	M	18	13	Special school, low IQ	NA	NA	
12	M	17	11	Normal school, maths difficult	NA	NA	Gorlin's
13	M	24	13	Normal school, remedial lessons	NA	NA	
14	M	6	9	Normal school, remedial lessons	NA	NA	
15	M	14	8	Normal school, maths difficult	NA	NA	
16	F	20	7	Normal school, maths and spelling difficult	NA	NA	

spans a very long time period during which better staging and assessment of patients have become routine and during which radiotherapy techniques and use of adjuvant chemotherapy have changed. The strength of the study is that it represents the longest reported follow-up on this important group of patients.

A relapse-free survival at 5 and 10 years of 54% and an actuarial survival of 44% has been achieved in patients with radiation administered to the craniospinal axis. These results have been achieved with a lower prescribed dose than is conventionally administered and compares favourably with young children treated in other series. This single institution experience cannot provide a recommendation for reduced craniospinal irradiation as this is properly the role of a randomised clinical trial. It should be noted that such a study undertaken by the POG

and CCSG groups testing reduced dose craniospinal radiotherapy was terminated because of an adverse outcome in the study arm (Study dose 23.4 Gy vs. standard dose of 36 Gy) [13]. This data is still relatively immature but there is some early information to suggest that the difference is reducing with longer follow-ups. Certainly in SIOP II [14] where low risk patients with medulloblastoma were randomised between standard or reduced dose radiotherapy (35 Gy vs. 25 Gy), no adverse outcome in terms of survival was noted unless the patients also received ''sandwich'' chemotherapy.

Whilst the majority of deaths occurred from disease and early treatment related toxicity, there were two additional contributory factors influencing longer term survival. These were BCNU induced pulmonary fibrosis [8,15] and secondary tumours in a patient with Gorlin's syndrome. The late deaths seen from pulmonary fibrosis were also seen in patients treated with BNCU for other brain tumours, and of five children treated with BCNU under the age of five at this institution, all are dead either from disease or lung toxicity. Clearly these deaths are avoidable if BCNU is not given during early childhood.

The second group of patients which have been identified as at risk of late death are those with Gorlin's syndrome. These patients account for 3–5% of all patients with medulloblastoma and are particularly prevalent in the younger age group. Of the three patients identified in the study two survived their medulloblastoma and of these one has died 30 years following treatment from multiple skin carcinomas. The second remains at risk 27 years from treatment and is alive with multiple tumours. This is an important group to screen for in any study, so that appropriate support and genetic counseling can be offered.

Although the technique of radiotherapy delivery changed over time, the philosophy at this institution was to administer a reduced dose of radiation to neuroaxis in the hope of ameliorating late effects. Consequently, the resulting late effects described for this cohort result from a median craniospinal dose of 30 Gy over 4 weeks (mean 27 Gy) in the megavoltage group, and 27 Gy in the kilovoltage group. Even at this dose the deleterious effect of craniospinal irradiation on growth was confirmed with contributory factors from spinal shortening, growth hormone deficiency, premature puberty, and hypothyroidism. Some of the impairment in linear growth may be preventable through appropriate endocrinological surveillance and intervention to delay onset of puberty, use of growth hormone, and treatment of hypothyroidism [16,17,18,19]. However, these supportive measures will also act to worsen the degree of spinal disproportion. How severe this problem is will become clearer as the younger survivors in this cohort reach final height. Unfortunately, it is unlikely that a radiation dose can be prescribed which will avoid the impact on spinal growth without compromising cure. The only alternative is to avoid spinal irradiation, implicit in the development of current chemotherapy strategies [4,20].

The tissue which is likely to benefit from any reduction in craniospinal dose is the brain where impairment in late neuropsychological function has been shown to be directly related to radiation dose [21,22,23]. Unfortunately, neuropsychological attainment and quality of patients' lives were the least well documented aspects of this retrospective analysis. Although ten of 16 patients attended main stream school, this is not an objective measure of school performance as social policy influenced school placement. This is reflected in the fact that all but one patient required extra teaching support. However it was surprising that two individuals had sought work and that one had maintained a job as a glass polisher. To complete the information on this patient group, a cross sectional study will be undertaken to look more carefully at neuropsychological deficit, social function, and patient and family perception of outcome.

Single institution studies in rare tumours always suffer from limitations produced by referral bias, changes in assessment, and management strategies over time. However, they can give insight into the long-term future of patients and it is these concerns that are currently influencing treatment approaches in young children with medulloblastoma. This study confirms the burden of long-term sequelae of treatment by irradiation, and highlights very late deaths from treatment related toxicity or from genetic predisposition. Continued monitoring and more extensive investigation of this cohort will provide useful baseline information on the health status of surviving adults treated for medulloblastoma as very young children, and will provide outcome measures against which newer treatments can be assessed.

CONCLUSIONS

This study demonstrates that for patients under 3 years old treated with ''standard treatment'' the outcome in terms of survival is the same as for older children but in terms of neuropsychological sequelae and growth effects these patients are disadvantaged. The addition of nitrosurea chemotherapy contributed to the morbidity and mortality of some patients in this group, in some cases long after treatment was administered.

Newer treatments aim to delay or avoid radiotherapy by the administration of chemotherapy. It may take many years, as for the patients in this series, to assess the full impact of such treatments on health status.

ACKNOWLEDGMENTS

Thanks to D Ryder for statistical assistance, Dr S Shalet for advice on growth data, Sister P Sutherland for

information on social attainments and V Blair (CRC Paediatric and Familial Cancer Research Group) for providing information from the Manchester Children's Tumour Registry. The Manchester Children's Tumour Registry is supported by the Cancer Research Campaign.

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